

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: H. Michael SHEPARD  
Title: ENZYME CATALYZED  
THERAPEUTIC COMPOUNDS  
Appl. No.: 10/681,418  
Filing Date: October 7, 2003  
Examiner: Crane, Lawrence E.  
Art Unit: 1623  
Confirmation No. 7416

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Mail Stop RCE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

**TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

**RELEVANCE OF EACH DOCUMENT**

All of the documents are in English.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

Respectfully submitted,

Date

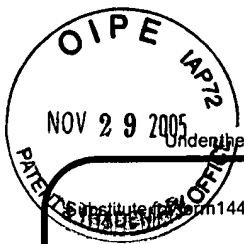
Nov. 29, 2005

By

Antoinette F. Konski

FOLEY & LARDNER LLP  
Customer Number: 38706  
Telephone: (650) 251-1129  
Facsimile: (650) 856-3710

Antoinette F. Konski  
Attorney for Applicant  
Registration No. 34,202



PTO/SB/08A (07-05)

Approved for use through 07/31/2006. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 1 of 1

**Complete if Known**

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	1623
Examiner Name	Crane, Lawrence E.
Attorney Docket Number	NB 2008.01; 060925-0801

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number – Kind Code <sup>2</sup> (if known)			
	1	US-6,589,941 B1	07-08-2003	Fahrig et al.	
	2	US-6,599,499	07-29-2003	Rosen et al.	
	3	US-6,677,314	01-13-2004	Klecker et al.	
	4	US-6,677,315	01-13-2004	Klecker et al.	
	5	US-6,682,715	01-27-2004	Klecker et al.	
	6	US-6,683,045	01-27-2004	Klecker et al.	
	7	US-6,703,374	03-09-2004	Klecker et al.	
	8	US-			
	9	US-			

**FOREIGN PATENT DOCUMENTS**

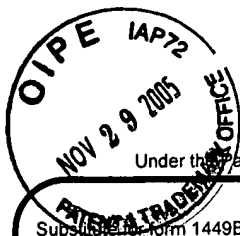
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup> – Number <sup>4</sup> – Kind Code <sup>5</sup> (if known)				
	10					
	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					

Examiner's  
SignatureDate  
Considered

\* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

The collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2.0 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing this form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Subsidiary Form 1449B/PTO

## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

### Complete if Known

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	1623
Examiner Name	Crane, Lawrence E.
Attorney Docket Number	NB 2008.01; 060925-0801

### NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T <sup>2</sup>
	1	BATHE et al. "Increased thymidylate synthase gene expression in liver metastases from colorectal carcinoma: implications for chemotherapeutic options and survival" <i>Cancer J. Sci. Am.</i> (1999) 5(1):34-40	
	2	BELT et al. "Nucleoside Transport in Normal and Neoplastic Cells" <i>Advan. Enzyme Regul.</i> (1993) 33:235-252	
	3	BIBLE et al. "Cytotoxic synergy between flavopiridol (NSC 649890, L86-8275) and various antineoplastic agents: the importance of sequence of administration" <i>Cancer Res.</i> (August 15, 1997) 57(16):3375-80	
	4	CHOU and TALALAY, "Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors" <i>Adv. Enzyme Regul.</i> (1984) 22:27-55	
	5	CURT "Cancer drug development: new targets for cancer treatment" <i>Oncologist</i> (1996) 1(3):II-III	
	6	CURTIN et al. "Mechanism of Cell Death following Thymidylate Synthase Inhibition: 2'-Deoxyuridine-5'-triphosphate Accumulation, DNA Damage, and Growth Inhibition following Exposure to CB3717 and Dipyridamole" <i>Cancer Res.</i> (May 1, 1991) 51:2346-2352	
	7	GOEL et al. "Selective Intraperitoneal Biochemical Modulation of Methotrexate by Dipyridamole" <i>J. Clin. Oncol.</i> (February 1989) 7(2):262-269	
	8	GORLICK et al. "Drug Resistance in Colon Cancer" <i>Semin. Oncol.</i> (December 1999) 26(6):606-611	
	9	GREM "Biochemical modulation of fluorouracil by dipyridamole: preclinical and clinical experience" <i>Semin Oncol.</i> (April 1992) 19(2 Suppl 3):56-65	
	10	GRIFFITH et al. "Differential Inhibition of Nucleoside Transport Systems in Mammalian Cells by a New Series of Compounds Related to Lidoflazine and Mioflazine" <i>Biochem. Pharmacol.</i> (1990) 40(10):2297-2303	
	11	KRAUPP et al. "Membrane Transport of Nucleobases: Interaction with Inhibitors" <i>Gen. Pharmacol.</i> (1995) 26(6):1185-1190	
	12	LACKEY et al. "Enzyme-catalyzed therapeutic agent (ECTA) design: activation of the antitumor ECTA compound NB1011 by thymidylate synthase" <i>Biochem. Pharmacol.</i> (2001) 61:179-189	
	13	LEHMAN et al. "Modulation of RTX cytotoxicity by thymidine and dipyridamole in vitro: implications for chemotherapy" <i>Cancer Chemother. Pharmacol.</i> (2000) 45:142-148	
	14	LEICHMAN et al. "Quantitation of Intratumoral Thymidylate Synthase Expression Predicts for Disseminated Colorectal Cancer Response and Resistance to Protracted-Infusion Fluorouracil and Weekly Leucovorin" <i>J. Clin. Oncol.</i> (October 1997) 15(10):3223-3229	
	15	LEICHMAN "Thymidylate synthase as a predictor of response" <i>Oncol.</i> (August 1998) 12(8Suppl.6):43-47	
	16	LENZ et al. "Rapid quantitative PCR for determination of relative gene expressions in tissue specimens" <i>PCR Methods Appl.</i> (1995) 4:305-308	

Examiner's  
Signature

Date  
Considered

\* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2
-------	---	----	---

*Complete if Known*

<i>Application Number</i>	<b>10/681,418</b>
<i>Filing Date</i>	<b>October 7, 2003</b>
<i>First Named Inventor</i>	<b>H. Michael SHEPARD</b>
<i>Art Unit</i>	<b>1623</b>
<i>Examiner Name</i>	<b>Crane, Lawrence E.</b>
<i>Attorney Docket Number</i>	<b>NB 2008.01; 060925-0801</b>

## NON PATENT LITERATURE DOCUMENTS

[illegible]

**Examiner's  
Signature**

Date Considered

\* **EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing this form, call 1-800-PTO-9199 and select option 2.*